TD-1211 Phase 2b Study Demonstrates Increased Bowel Movement Frequency in Patients with Opioid-induced Constipation Regardless of Baseline Opioid Dose

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Introduction

- Opioid analgesics such as morphine continue to play a critical role in chronic cancer and non-cancer pain control.[1] Despite their effectiveness, opioids have significant drawbacks, notably the development of analgesic tolerance and physical dependence, sedation, respiratory depression and bowel dysfunction.[2]
- Opioid-induced constipation (OIC) is common, affecting up to 80% of patients receiving opioids for chronic non-cancer pain.[3]
- TD-1211 is an investigational, peripherally selective, multivalent mu-opioid receptor antagonist designed to alleviate gastrointestinal side effects of opioid therapy without affecting analgesia.
- Safety and efficacy results, including the primary and key secondary endpoints, from a 5-week, Phase 2b study in chronic non-cancer pain OIC patients have been previously reported.[4]
- Since patients with chronic non-cancer pain take a wide range of opioid doses, patients were divided into low and high baseline opioid dose groups (<100 and ≥100 MEU) to explore if baseline opioid dose impacts TD-1211 treatment response.

Methods

- A 5-week, double-blind, randomized, multi-center, placebo-controlled, parallel-group study was conducted in chronic non-cancer pain patients with OIC, defined as ≤5 spontaneous bowel movements (SBMs) over a 2-week baseline period and at least one additional symptom of constipation in at least 25% of the bowel movements.
- For the first 4 days of dosing, patients randomized to TD-1211 received 5mg daily and on Day 5, remained at 5mg or were dose-escalated to 10mg or 15mg daily for the remainder of the treatment period. Patients randomized to placebo received placebo for all 5 weeks.
- For at least 14 days prior to Day 1, patients were on a stable chronic opioid regimen, with a total daily dose of ≥30mg morphine equivalent units (MEU).
- Patients were required to stop laxatives and bowel regimens, except protocol-permitted rescue bisacodyl use, throughout the study.
- Electronic diaries collected frequency, timing, and symptoms of bowel movements; use of laxatives and opioids; daily pain scores; and satisfaction/ quality of life metrics.
- Primary efficacy endpoint was the change from baseline in weekly average complete spontaneous bowel movements (CSBMs) over weeks 2-5 of treatment.
- Key secondary endpoint was the change from baseline in weekly average spontaneous bowel movements (SBMs) over the same period.
- Week 1 was excluded from the primary analysis in order to confirm the durability of response and predictability of longer term efficacy studies.
- Patients were divided into low and high baseline opioid dose groups (<100 and ≥100 MEU) and evaluated on the study's primary and key secondary endpoints.

Results

Patient baseline demographics

- As shown in Table 1, baseline characteristics were similar for all treatment groups in the overall population as well as the low and high baseline opioid dose groups.
- Subjects were on a representative spectrum of opioids.
- Daily opioid doses ranged from 30-1740 oral MEU.
- Back pain was the most commonly reported reason for chronic opioid use.
- Mean duration of OIC ranged from 5.3 to 6.7 years.

Table 1: Patient Baseline Demographics by Baseline Opioid Use

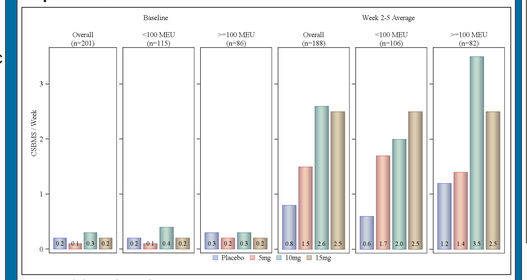
Overall Population			TD-1211	
	Placebo (N=54)	5 mg (N=55)	10 mg (N=53)	15 mg (N=53)
Mean Age (years)	47.6	48.3	49.2	48.9
Female Gender	28	37	32	30
BMI Mean (kg/m^2)	28.3	27.8	27.8	28.1
Mean Daily MEUs (mg)	118.3	189.4	145.7	124.8
Baseline Opioid Dose <100 MEU			**TD-1211**	
	Placebo (N=33)	5 mg (N=27)	10 mg (N=29)	15 mg (N=29)
Mean Age (years)	46.3	48.4	48.8	48.5
Female Gender	20	19	15	17
BMI Mean (kg/m^2)	28.9	27.7	27.5	28.1
Mean Daily MEUs (mg)	53.4	54.7	51.6	57.1
Baseline Opioid Dose ≥100 MEU			**TD-1211**	
	Placebo (N=21)	5 mg (N=28)	10 mg (N=24)	15 mg (N=24)
Mean Age (years)	49.8	48.1	49.6	49.3
Female Gender	8	18	17	13
BMI Mean (kg/m^2)	27.3	27.9	28.0	28.2
Mean Daily MEUs (mg)	220.1	319.4	259.4	206.5

Modified Intent to Treat Population

Efficacy Endpoints by Baseline Opioid Dose Group

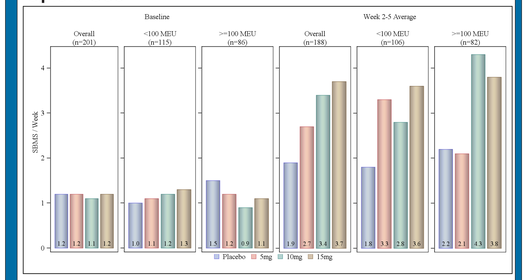
- The baseline frequency of CSBMs and SBMs was similar for low and high baseline opioid daily average MEUs (Figs. 1-2).
- There was a dose-response relationship between CSBM and SBM frequency across the range of opioids received in the overall patient population and in patients receiving < 100 daily MEUs of opioid (Figs. 1-2).
- Average CSBMs ands SBMs during weeks 2-5 were similar for the placebo and 5 mg TD-1211 arms of the study in patients receiving greater than 100 daily MEUs (Figs. 1-2).

Figure 1: Baseline and Weeks 2-5 Average Complete Spontaneous Bowel Movements (CSBMs) by Baseline Opioid Use



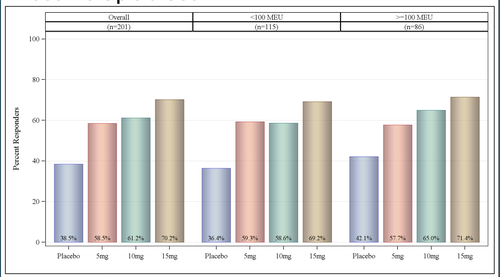
EA population; no imputation

Figure 2: Baseline and Weeks 2-5 Average Spontaneous Bowel Movements (SBMs) by Baseline Opioid Use



EA population; no imputation

Figure 3: Pre-Specified SBM Responder Analysis by Baseline Opioid Use



EA population with Non-Responder Imputation for subjects with missing response.

- Responder definition: ≥3 SBMs per week and an increase of ≥ 1 SBM per week from baseline for ≥3 weeks over Weeks 2-5

Table 2: Mean Change from Baseline in Weeks 2-5 Weekly Average CSBMs and SBMs by Baseline Opioid Use

	Mean Change from Baseline in Weekly Average CSBMs				Mean Change from Baseline in Weekly Average SBMs			
	Placebo	5mg TD-1211	10mg TD-1211	15mg TD-1211	Placebo	5mg TD-1211	10mg TD-1211	15mg TD-1211
Overall	0.8 (n=52)	1.5 (n=53) p=0.0413	2.6 (n=49) p=0.0010	2.5 (n=47) p=0.0003	1.9 (n=52)	2.7 (n=53) p=0.0739	3.4 (n=49) p=0.0038	3.7 (n=47) p=0.0003
<100 MEU	0.6 (n=33)	1.7 (n=27)	2.0 (n=29)	2.5 (n=26)	1.8 (n=33)	3.3 (n=27)	2.8 (n=29)	3.6 (n=26)
≥100 MEU	1.2 (n=19)	1.4 (n=26)	3.5 (n=20)	2.5 (n=21)	2.2 (n=19)	2.1 (n=26)	4.3 (n=20)	3.8 (n=21)

Table 3: GI-Related Adverse Events Occurring in at Least 2 Patients in Any Group

Safety Population	TD-1211				
	Placebo (N=54)	5 mg (N=56)	10 mg (N=53)	15 mg (N=52)	All TD-1211 (N=161)
No. of Patients and Percentage with GI AEs	11 (20.4%)	13 (23.2%)	15 (28.3%)	14 (26.9%)	42 (26.1%)
Abdominal Pain	6 (11.1%)	7 (12.5%)	6 (11.3%)	8 (15.4%)	21 (13.0%)
Abdominal Pain Upper	1 (1.9%)	2 (3.6%)	3 (5.7%)	2 (3.8%)	7 (4.3%)
Diarrhea	0	4 (7.1%)	6 (11.3%)	4 (7.7%)	14 (8.7%)
Flatulence	3 (5.6%)	1 (1.8%)	2 (3.8%)	1 (1.9%)	4 (2.5%)
Nausea	2 (3.7%)	4 (7.1%)	8 (15.1%)	3 (5.8%)	15 (9.3%)
Vomiting	1 (1.9%)	4 (7.1%)	1 (1.9%)	0	5 (3.1%)

Efficacy Endpoints by Baseline Opioid Dose (con't)

- Using a pre-specified responder definition, there was a dose response relationship between responder rate and TD-1211 dose that was independent of patient daily opioid dose (Fig. 3).

Tolerability and Safety

- TD-1211 was generally well tolerated, with overall treatment emergent adverse events (TEAEs) similar between TD-1211 and placebo and gastrointestinal (GI) TEAEs predominant (Table 1).
- The majority of GI-related AEs were associated with treatment initiation, mild-to-moderate, and resolving within a few days.
- No treatment-related serious adverse events (SAEs) were reported.
- No clinically significant laboratory, ECG, or vital sign abnormalities were observed.

TD-1211 Conclusions

- 10mg and 15mg demonstrated a clinically meaningful, sustained response in CSBM and SBM frequency over the duration of the treatment period in OIC patients irrespective of baseline opioid dose.
- Generally well-tolerated with no treatment-related SAEs.
- Majority of treatment-related GI AEs were associated with initiation of treatment, resolved within a few days, and were mild or moderate.

References

1. Walsh, T.D. (2000). Seminars in Oncology, 27, 45-63.
2. Walsh, T.D. (1990). J. Pain Symptom Manage., 5, 362-367.
3. Holzer, P. (2012). Current Pharmaceutical Design, 18, 6010-6020.
4. Vickery, R., et al. PainWeek 2012, Las Vegas, NV, September 5-8. Poster #121.